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PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/148,012	KRIEGER, MONTY	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,15,16 and 19-22* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,15,16 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Amendment after Appeal, filed 5/31/05, has been entered into the record.

B. Claims 1-10, 12, 15, 16 and 19-22 are pending. Claim 19 is withdrawn as being drawn to a non-elected invention. Therefore, claims 1-10, 12, 15, 16 and 20-22 are the subject of this Office Action.

C. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Board Decision Regarding 35 USC § 112, first paragraph – new matter

A. . The Board of Patent Appeals and Interferences rendered a decision on 3/29/05 which contains a new ground of rejection pursuant to 37 CFR 41.50(b). This new matter rejection was addressed by Appellants in their response filed 5/31/05. In their response, Appellants amended claim 1 to recite limitations now supported in the specification as originally filed. Therefore, the new matter rejection by the Board has been overcome.

3. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 1-10, 12, 15, 16 and 20-22 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of inhibiting pregnancy or decreasing production of steroids in a mammal by administering a compound affecting SR-BI. In the Remarks dated 5/31/05, Applicants argue that they are the first to recognize that SR-BI plays a major role in female reproduction and demonstrated this using knock-out mice. These mice are unable to carry a fetus to term. Applicants have shown that treatment of these mice with the cholesterol-lowering agent, probucol, restores fertility to these animals; therefore, showing that SR-BI is essential for normal female fertility.

Applicants' arguments have been considered, but are not deemed persuasive. The only adequately described example in the specification is that completely knocking out the SR-BI gene (i.e. from all

tissues) causes female mice to be infertile (Example 6). The present claims are genus claims. First, the claims encompass a universe of compounds used to inhibit pregnancy. Applicants argue that the disclosure of estrogen, a vector encoding SR-BI and an anti-SR-BI antibody provide broad support for a genus claim. However, though these compounds have been shown to alter cholesterol levels in a mammal, they have not been shown to inhibit pregnancy.

In addition, Applicants argue that they have disclosed an extensive list of molecules on page 11 of the specification which inhibit SR-BI. However, this list includes molecules which bind SR-BI and compounds which block binding of HDL to SR-BI. It is these groups of compounds which lack the greatest written description. Applicants have only identified estrogen as belonging to one of these classes. Based on this, Applicants are claiming methods using any molecules which bind SR-BI and compounds which block binding of HDL to SR-BI. Though Applicants are claiming methods, and not the compounds themselves, Applicants still have not provided any written description of these compounds, or any effective amounts to inhibit pregnancy in a mammal, nor have Applicants shown that any of these compounds, or antibodies, or nucleic acids, are effective in this treatment.

Applicant has only provided written description of a small number of specific compounds which act via SR-BI, including estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification) to alter cholesterol levels. Applicant has provided no written description of any compounds which would inhibit pregnancy in a fully formed female mammal other than the use of probucol to improve fertility in knock-out mice.

Furthermore, the claims read on altering SR-BI receptors, or affecting receptor binding in *any* tissue. Appellant has not provided adequate written description of which specific tissues modulation of SR-BI would be required in order to inhibit pregnancy. Again, Applicant has only demonstrated that completely knocking out the SR-BI gene (i.e. from all tissues) causes female mice to be infertile (Example 6). However, in the other examples in the specification, Applicant does not describe how altering SR-BI levels in these tissues alone affects pregnancy in a mammal, or if altering SR-BI levels *at all* in these tissues is sufficient to inhibit pregnancy. For example, in Examples 3 and 4, Applicants have only shown that estrogen-treated rats show an upregulation of SR-BI in adrenal membranes (page 39, line 30 – page 40, line 1) and ovaries (page 40, lines 20-23). Applicants have also demonstrated the effect of hepatic SR-BI overexpression on plasma cholesterol levels (Example 4, especially page 41, lines 12-14 and Table 1). Again, no nexus between SR-BI expression in these tissues and the ability to inhibit pregnancy in a fully formed, normal (i.e. non-transgenic) mammal has been described. In other words,

knocking out the SR-BI gene in an embryonic stem cell does not demonstrate that Applicants were in possession of a method of inhibiting pregnancy in any other system other than a transgenic female animal. The examples in the specification only show that Applicants were in possession of compounds which alter cholesterol levels, not which inhibit pregnancy. Therefore, though Applicants may be correct in stating that "one of ordinary skill in the art will readily recognize not only the direct correlation that exists between cholesterol/HDL and the existence of SR-BI, but also the many compounds that already exist for regulating cholesterol levels," Applicants, respectfully, have only demonstrated just that. They have not demonstrated that they are able to perform the claimed methods, but have only demonstrated a relationship between cholesterol and SR-BI. This can further be seen by comparing claims 4 and 5 as well as 6 and 7. Claims 4 and 6 recite decreasing SR-BI levels, whereas claims 5 and 7 recite increasing SR-BI levels. Therefore, it is not understood how Appellants have adequately supported the present invention when the claims recite either an increase or decrease in SR-BI levels. This adds further support that Applicants were not in possession of the claimed invention since it is not known in which direction SR-BI must be altered in order to inhibit pregnancy.

Therefore, though Applicants have taught a method of screening for compounds which inhibit pregnancy, as well as a method of drug design, these are general concepts, as no compounds have been described which can be used in the claimed invention, other than probucol in knock-out female mice. The teachings of Miettinen et al. have been considered and, though a link between cholesterol and fertility may have been established, the present specification still does not adequately describe compounds which perform the claimed function.

4. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. Claims 1-10, 12, 15, 16 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for improving fertility in female mice by administering probucol after knocking out the SR-BI gene (i.e. from all tissues), does not reasonably provide enablement for inhibiting pregnancy in any other animal models by altering SR-BI. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of inhibiting pregnancy or decreasing production of steroids in a mammal by administering a compound affecting SR-BI. In the Remarks dated 5/31/05, Applicants argue that they are the first to recognize that SR-BI plays a major role in female reproduction and demonstrated this using knock-out mice. These mice are unable to carry a fetus to term. Applicants have

shown that treatment of these mice with the cholesterol-lowering agent, probucol, restores fertility to these animals; therefore, showing that SR-BI is essential for normal female fertility.

Applicants argue on pages 3-5 of the Response dated 7/17/01, that the key to the present invention is the evolutionary conservation between mouse and human SR-BI and that this conservation allows for familiar and routine experimentation, via the various assays cited on page 3 of Applicant's response, dated 7/17/01 as routine in the art, to be conducted by one of skill in the art. The Applicant also argue that this evolutionary conservation also allows for careful extrapolation of the results obtained from such experimentation. Applicant further argues that ligands that bind SR-BI have been described and characterized (e.g. AcLDL, LDL, estrogen, HDL and SR-BI antibodies), that the full-length DNA encoding SR-BI is disclosed in the present specification and that the targeted sequence encoding SR-BI defines the complementary nature of the compounds to be designed. Similar arguments are made on pages 4-5 of the Response of Amendment D, filed 2/12/02 where Applicant argues that the data in the application (Examples 3, 5, 6 and 8) demonstrate that multiple compounds can be used to achieve the method of claim 1. They further support their argument by citing Miettinen et al. (J. Clin. Invenst. 108:1717-1722, 2001), who teach that SR-BI knockout mice are infertile and that fertility was restored by inactivating the apoI gene or administering the cholesterol lowering drug, probucol. However, while these results are interesting, the infertility in these mice was induced by genetic manipulation of an embryonic stem cell. There is no evidence of any female reproductive disorder, including in humans, which acts via SR-BI. Applicant has produced a specific genetic alteration in a stem cell to produce this infertility in female mice and have provided no nexus between a method of restoring fertility in female knock-out mice by administering probucol and a method of inhibiting pregnancy by modulating SR-BI in a fully formed, normal female mammal (i.e. which is not an SR-BI knockout). Furthermore, the last line of the abstract of Miettinen et al. is speculative in stating that abnormal lipoprotein metabolism may contribute to some form of human infertility. There is no evidence that altering SR-BI levels in a fertile female with normal SR-BI levels will have the desired effect of the claimed method. Finally, as further evidence for the lack of enablement of the present invention, there is no evidence in the art that women taking cholesterol-lowering drugs experience any fertility problems, demonstrating that cholesterol-lowering drugs, which would meet the limitation of claim 1, may not alter fertility (e.g inhibit pregnancy).

In considering Applicant's arguments regarding the examples in the specification demonstrating that various compounds bind SR-BI, the Examiner agrees that the specification does disclose various compounds which bind SR-BI, such as estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI

antibody (Example 8 on pages 55-66 of the specification). However, these compounds have only been shown to affect SR-BI and to alter cholesterol and lipoprotein levels, not to inhibit pregnancy in a normal female mammal. However, as stated by the Examiner in the previous paragraph, knocking out the SR-BI gene in an embryonic stem cell does not enable the artisan to inhibit pregnancy in a fully formed mammal by administering a compound which modulates SR-BI.

The instant fact pattern is similar to that in *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), wherein a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

Furthermore, the claims of the present invention recite, or read on, altering SR-BI receptors in *any* tissue. Applicant has provided no guidance or working examples of which specific tissues modulation of SR-BI would be required in order to inhibit pregnancy. Again, Applicant has only demonstrated that completely knocking out the SR-BI gene (i.e. from all tissues) causes female mice to be infertile (Example 6). In Examples 3 and 4, Applicant has only shown that estrogen-treated rats show an upregulation of SR-BI in adrenal membranes (page 39, line 30 – page 40, line 1) and ovaries (page 40, lines 20-23). Applicant has also demonstrated the effect of hepatic SR-BI overexpression on plasma cholesterol levels (Example 4, especially page 41, lines 12-14 and Table 1). However, no nexus between SR-BI expression in these tissues and the ability to inhibit pregnancy has been made. It would also be unpredictable to one of ordinary skill in the art how to inhibit pregnancy in a "normal" female by modulating SR-BI.

Finally, Applicants argue in the Appeal Brief filed 9/15/03 that the specification is replete with support for a connection between cholesterol levels and fertility. Because of Applicans' novel discovery, they argue that they are entitled to all compounds which alter lipoprotein or cholesterol levels for the purpose of altering fertility in a mammal and that the class of patients encompassed by the claims is relatively small. While it may be true that the class of patients is relatively small and may not overlap other groups of patients, the fact remains that Applicants have not demonstrated that they are in possession of the claimed invention. Applicants have only demonstrated that they are in possession of compounds which alter cholesterol and that fertility can be restored in transgenic mice lacking the SR-BI gene by administering cholesterol-lowering drugs. This would likely be acceptable if Applicants were

claiming a method of increasing fertility in transgenic mice lacking the SR-BI gene, or methods of altering cholesterol levels by modulating the SR-BI receptor, but this is not the case. Applicants have taken their one example using a transgenic mouse and, respectfully, basically combined it with their in vitro data using antibodies and estrogen to conclude that these cholesterol-lowering drugs can inhibit pregnancy, when the specification does not enable this. This can further be seen in the claims. Claims 4 and 6 recite decreasing SR-BI levels, whereas claims 5 and 7 recite increasing SR-BI levels. Therefore, it is not understood how Applicants have adequately supported the present invention when the claims recite either an increase or decrease in SR-BI levels. This adds further support for a lack of enablement since Appellants are not able to specify in which direction SR-BI must be altered in order to treat a specific disease, or to alter fertility.

In summary, the breadth of the claims is excessive regarding a method for inhibiting pregnancy in a mammal comprising administering *any* compound altering SR-BI in the mammal in *any* specific tissue. Applicants have only shown that a complete knockout of the SR-BI gene alters fertility in female mice and that probucol can restore this fertility. There is also a lack of guidance or working examples of any compounds, other than probucol, which have been shown to improve fertility. These factors, in addition to the lack of predictability of how to extrapolate knock-out data to "normal" mice, or other mammals, lead the Examiner to hold that undue experimentation is necessary to practice the claimed invention.

5. Claim Rejections - 35 USC § 112, second paragraph

A. All rejections under 35 USC 112, second paragraph, have been withdrawn in view of the Board Decision dated 3/29/05.

6. Conclusion

A. No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on T-F 10 AM – 7 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER

Robert Landsman
Primary Examiner
Art Unit 1647